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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/727,030	11/30/2000	Patrick N. Gilles	612,404-370	3744

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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 02/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/727,030	GILLES ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-14 and 16-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-14 and 16-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/28/01 & 1/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action responds the Amendment received on November 5, 2004.

Information Disclosure Statement

The non-patent literatures cited in IDS received on February 28, 2001 and January 26, 2004, previously not-considered, have now been considered.

The signed copies of their PTO-1449 are attached hereto.

Claim Objections

The objection of claim 10 for containing grammatical error, made in the Office Action mailed on May 3, 2004, is withdrawn in view of the Amendment received on November 5, 2004, amending the claim.

Claim Rejections - 35 USC § 112

The rejection of claim 2 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on May 3, 2004 is withdrawn in view of the Amendment received on November 5, 2004, amending the claim.

Claim Rejections - 35 USC § 102

The rejection of claims 1-5, 7-9, 12-14, 16, 17, and 19-21 under 35 U.S.C. 102(e) as being anticipated by Nerenberg et al. (U.S. Patent No. 6,468,742 B2, issued October 22, 2002, priority February 25, 1998), made in the Office Action mailed on May 3, 2004 is withdrawn in view of the Amendment received on November 5, 2004, amending the independent claims to incorporate the limitations of claims 10 and 15.

Claim Rejections - 35 USC § 103

The rejection of claim 6 under 35 U.S.C. 103(a) as unpatentable over Nerenberg et al. (U.S. Patent No. 6,468,742 B2, issued October 22, 2002, priority February 25, 1998) in view of Fodor et al. (U.S. Patent No. 6,309,823 B1, issued October 30, 2001, filed January 3, 1997), made in the Office Action mailed on May 3, 2004 is withdrawn in view of the Amendment received on November 5, 2004, amending the independent claim to incorporate the limitation of claim 10 and 15.

The rejection of claims 10 and 15 under 35 U.S.C. 103(a) as being unpatentable over Nerenberg et al. (U.S. Patent No. 6,468,742 B2, issued October 22, 2002, priority February 25, 1998) in view of Heller et al. (U.S. Patent No. 6,048,690, issued April 11, 2000, filed May 14, 1997), made in the Office Action mailed on May 3, 2004 is withdrawn in view of the Amendment received on November 5, 2004, canceling said claims 10 and 15.

New Grounds – Necessitated by Amendment

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7-9, 12-14, and 16, 17, and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nerenberg et al. (U.S. Patent No. 6,468,742 B2, issued October 22,

2002, priority February 25, 1998)[1] in view of Heller et al. (U.S. Patent No. 6,048,690, issued April 11, 2000, filed May 14, 1997)[2].

Nerenberg et al. disclose a method of using an electronically addressable array for the purpose of detecting Single Nucleotide Polymorphism (Abstract). The method disclosed by Nerenberg et al. involves the following steps:

a) providing at least one sample nucleic acid containing at least one target nucleic acid (column 16, lines 22-25) on a electronically addressable array;

b) electronically biasing one or more specified test sites (column 6, lines 25-27);

c) immobilizing the target nucleic acid to the test sites by avidin/streptavidin interaction (column 6, lines 25-27; column 16, lines 40-44);

d) electronically hybridizing a first and second probes to the immobilized nucleic acid, wherein the first probe is specific for a wild-type allele and the second probe is specific for a mutant (*i.e.,* polymorphic) allele (column 16, lines 30-36), each labeled with different labels (column 7, line 52-53; column 17, line 60), such as cy3 and cy5 (column 13, line 61);

e) performing electronic stringency on the hybridized complexes (column 6, lines 43-58); and

f) detecting the hybridization complexes (column 16, lines 64-67),

thereby meeting the limitations of instant claims 1, 7, 13, and 14.

Nerenberg et al. disclose that the target nucleic acid can be amplified prior to their immobilization (column 16, line 24), thereby meeting the limitation of instant claim 2.

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[1] cited previously in the Office Action mailed on May 3, 2004.
[2] cited previously in the Office Action mailed on May 3, 2004.

At least one wild-type and single nucleotide polymorphism is identified by the method of Nerenberg et al., (therefore, at least bi-allelic) and wherein all possible single polymorphism could be detected (column 20, lines 36-40), thereby meeting the limitations of claims 3, 4, and 12. The target nucleic acid is also disclosed as being from Mannose Binding protein gene locus that correlates with susceptibility to sepsis in leukopenic patients (column 21, lines 63-66), or in human HLA (or major histocompatibility complex proteins) (column 22, lines 1-6), thereby meeting the limitation of claim 5.

The method employed by Nerenberg et al. minimizes the mismatches that occur between the target sequence and its hybridization probes (column 6, lines 54-67; column 17, lines 35-40; Figure 9) to minimize false positives (or reducing the signals from mismatched probes to a background level), thereby meeting the limitations of claims 8 and 9.

At least two different SNPs (Hemocromatosis locus and Factor V locus) are identified from a sample in the multiplex analysis of target sequences (column 20; Figure 12), thereby anticipating instant claim 16. The method involves an electronic hybridization of the probes for Hemocromatosis, followed by their stripping, further followed by the electronic hybridization of the probes for Factor V (column 20, lines 10-15), thereby meeting the limitations of claims 19-21.

Additionally, the method of Nerenberg et al. allows the hybridization of the probes and the target nucleic acids prior to the immobilization of the target nucleic acids to the test sites (as evidenced by claims 1 and 2 of Nerenberg et al.), thereby meeting the limitation of instant claim 17.

While Nerenberg et al. employ the use of a stabilizer probe to preclude self-complemtarity of the double-stranded target nucleic acid to enhance probe hybridization, the instant claims "comprises" the steps recited therein, allowing for inclusion of other ingredients.

Heller et al. disclose a method of employing the same electronically addressable array of Nerenberg et al. for the purpose of determining the FPE, or fluorescent perturbation effect, which is a powerful analytical tool for efficient discrimination of match/mismatch DNA hybrids (column 5, lines 15-20). The method involves the monitoring of the relative fluorescent intensity of the hybridized probes with respect to the voltage applied (Figure 1A and 1B, therefore meets instant claims 10 and 11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Nerenberg et al. with that of Heller et al. to arrive at the claimed invention for the following reasons.

Nerenberg et al. recognize the importance of being able to distinguish between the match and mismatched probes, wherein the artisans state:

"Moreover, electronic biasing equally facilitates distinguishing hybridization mismatches occurring at the terminal nucleic acid pairs of a hybridized duplex as well as destabilizing mismatches occurring internally...allow[ing] the current invention to be less restricted in choices for positioning the location of SNP bases on probes..." (column 6, lines 54-61).

Heller et al. disclose that the fluorescent signal from labeled probes or target DNAs was perturbed during the initiation of electronic dehybridization (or stringency) ***at or around the electronic power levels (current and voltage)*** resulting as a, "rise or spike in the fluorescence intensity prior to dehybridization of the fluorescent labeled probe sequence from the DNA

sequence attached to the microscopic test site (column 10, lines 40-49), allowing the match/mismatch discrimination of the probes to be carried out, "***very rapidly***...compared to classical hybridization stringency process...." (column 11, lines 1-5).

Therefore, one of ordinary skill in the art would have been motivated to adopt the teachings of Heller et al., who employ the same electronically addressable array as Nerenberg et al. to arrive at the method of determining the FPE, for the advantage of efficiently discriminating the match and mismatch of probes-target duplex (*i.e.,* further improving the mismatch discrimination already recognized by Nerenberg et al.) with a reasonable expectation of success.

With regard to whether the plurality of sample nucleic acids from each patient samples are immobilized on one test site or different test sites, and whether each sample nucleic acid of from each patient sample comprises a different SNP locus, such is an obvious design modification that is considered to be well within the purview of an ordinarily skilled artisan in the array design (*i.e.,* Affymetrix^{TM}).

Finally, with regard to the patient sample nucleic acids, after their hybridization to their probes, being sequentially immobilized onto the test sites, as all nucleic acids must first be immobilized on to the test sites prior to their detection, one of ordinary skill in the art would have recognized that the probe-target hybridization duplex, had to be sequentially immobilized on to their test site for the subsequent detection method with a reasonable expectation of success.

In *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342 (CCPA 1968), the court expressed that, "in considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inference which one skilled in the art would reasonably be expected to draw therefrom."

In responding to Applicants' arguments stating that Affymetrix uses a system in which the capture probes are immobilized to the array not the sample nucleic acids (on page 9, 1st paragraph, Response), the example provided in the Office Action was solely intended to demonstrate whether the immobilized nucleic acids are immobilized on a single test site or across a plurality of different test sites was well-within the purview of an ordinarily skilled artisan. Applicants are reminded that in addition to Affymetrix microarrays, there is a host of well-known solid-substrate arrays which employ immobilized target nucleic acids on a solid-substrate (*i.e.,* ASO).

Therefore, it is maintained that whether an ordinarily skilled artisan would be inclined to immobilize all of the oligonucleotides on a single reaction site versus across a plurality of different reaction sites, such would be well-within the purview of said ordinarily skilled artisan.

Therefore, for the above reasons, the claims are *prima facie* obvious over the cited references.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nerenberg et al. (U.S. Patent No. 6,468,742 B2, issued October 22, 2002, priority February 25, 1998) in view of Heller et al. (U.S. Patent No. 6,048,690, issued April 11, 2000, filed May 14, 1997) as applied to claims 1-5, 7-9, 12-14, and 16, 17, and 19-21 above, and further in view of Fodor et al. (U.S. Patent No. 6,309,823 B1, issued October 30, 2001, filed January 3, 1997).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37

CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The teachings of Nerenberg et al. and Heller et al. have already been discussed above.

Nerenberg et al. and Heller et al. do not disclose a method of employing at least one control target nucleic acid.

Fodor et al. disclose a method of detecting polymorphisms via use of an oligonucleotide arrays, wherein the array contains control probes, for the purpose of gauging the background intensity level (column 10, lines 31-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the well known technique of employing control probes on a microarray of Nerenberg et al. and Heller et al. for the obvious benefit of accounting for background (or noise level) prevalent in a hybridization assay. One of ordinary skill in the art

would have had a reasonable expectation of success in combining the teachings as the use of control probes in the array hybridization, as demonstrated by Fodor et al., have been well-established in the art.

MPEP, at 2143.02, states that the prior art can be modified or combined to reject claims as obvious as long as there is a reasonable expectation of success. Given that the use of control probes in microarray for the benefit of accounting for background hybridization has been well-established, one of ordinary skill in the art microarray would have had a reasonable expectation of the success at arriving at the claimed invention, rendering the claims obvious over the cited references.

Therefore, for the above reasons, the invention as claimed is *prima facie* obvious over the cited references.

Rejections – Maintained

The rejection of claims 11 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nerenberg et al. (U.S. Patent No. 6,468,742 B2, issued October 22, 2002, priority February 25, 1998) in view of Heller et al. (U.S. Patent No. 6,048,690, issued April 11, 2000, filed May 14, 1997), made in the Office Action mailed on May 3, 2004 is maintained for the reasons of record.

Applicants' arguments received on November 5, 2004 have been fully considered but they are not found persuasive for the following reasons.

Preliminarily, Applicants are advised that claims 11 and 18 were rejected along with claims 10 and 15 as being obvious over the above cited references. Hence, the rejection is

properly maintainable although claim limitations of claims 10 and 15 were incorporated into independent claim 1.

Applicants argue that Affymetrix uses a system in which the capture probes are immobilized to the array not the sample nucleic acids (on page 9, 1st paragraph, Response), the example provided in the Office Action was solely intended to demonstrate whether the immobilized nucleic acids are immobilized on a single test site or across a plurality of different test sites was well-within the purview of an ordinarily skilled artisan. Applicants are reminded that in addition to Affymetrix microarrays, there is a host of well-known solid-substrate arrays which employ immobilized target nucleic acids on a solid-substrate (*i.e.,* ASO).

Therefore, it is maintained that whether an ordinarily skilled artisan would be inclined to immobilize all of the oligonucleotides on a single reaction site versus across a plurality of different reaction sites, such would be well-within the purview of said ordinarily skilled artisan.

Therefore, for the above reasons, the claims are *prima facie* obvious over the cited references.

Double Patenting - Withdrawn

The rejection of claims 1-5, 7-9, 12-14, 16, 17, and 19-21 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 12, 14, 16, 22, 32, and 33 of U.S. Patent No. 6,468,742 B2 (hereto referred to as '742 patent), made in the Office Action mailed on May 3, 2004 is withdrawn in view of the Amendment received on November 5, 2004, amending the independent claim to incorporate the limitation of claim 10 and 15.

The rejection of claim 6 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6,468,742 B2 (hereto referred to as '742 patent in view of Fodor et al. (U.S. Patent No. 6,309,823 B1, issued October 30, 2001, filed January 3, 1997), made in the Office Action mailed on May 3, 2004 is withdrawn in view of the Amendment received on November 5, 2004, amending the independent claim to incorporate the limitation of claim 10 and 15.

Rejection – Necessitated by Amendment

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 7-9, 12-14, 16, 17, and 19-21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6,468,742 B2 (hereto referred to as '742 patent) in view of Heller et al. (U.S. Patent No. 6,048,690, issued April 11, 2000, filed May 14, 1997).

Claim 1 of the '742 patent is drawn to a method for determining the presence of a specific sequence in at least one genetic locus of one or more target nucleic acids of interest in at

least one sample of interest using an electronically addressable capture sites with associated electrodes, the method comprising the following recited steps:

a) contacting a single stranded target nucleic acid of interest with at least one stabilizer oligonucleotide, said stabilizer oligonucleotide hybridizing to or adjacent to a region of expected variance in the target nucleic acid;

b) contacting the target nucleic acid of interest with at least one reporter oligonucleotide, comprising a sequence complementary to at least a portion of the target nucleic acid of interest;

c) electronically addressing the target nucleic acid to at least one capture site on the bioelectronic microchip, wherein the target nucleic acid is captured at the capture site by a capturing means;

d) after (a), (b), and (c), subjecting the hybridized complex to destabilizing conditions;

e) detecting the hybridization of the reporters oligonucleotide to the target nucleic acid.

Claim 2 of the '742 patent then recites that step (c) is conducted prior to steps (a) and (b), which results in the instant claim 1. While the claims do not explicitly state that the variance is a polymorphism, the specification of '742 is drawn to the method of identifying SNPs (as already discussed above), rendering instant claims 1 and 12 obvious.

Claim 22 of the '742 patent recites the obvious step of amplifying the target nucleic acids, meeting the limitation of instant claim 2.

With regard to the SNP locus being bi-allelic or multi-allelic as in instant claims 3 and 4, such is obvious in view of the disclosure on column 20, lines 36-40 of the '742 patent, which allows the identification of at least one wild-type and single nucleotide polymorphism or all possible single polymorphism.

With regard to the method being directed to detecting SNPs from nucleic acid of instant claim 5, such is obvious in view of the disclosed nucleic acid species – Mannose Binding protein gene locus that correlates with susceptibility to sepsis in leukopenic patients (column 21, lines 63-66), or in human HLA (or major histocompatibility complex proteins) disclosed in column 22, lines 1-6 of the '742 patent.

With regard instant claim 7, claim 12 of the '742 patent recites that the sample nucleic acid comprising a biotin moiety is immobilized on the capture site of the array based on biotin-binding moiety present at a capture site, wherein said interaction is disclosed as being biotin-streptavidin interaction in column 16, lines 40-44 of the '742 patent, rendering instant claim obvious.

With regard to instant claims 8 and 9, such steps are obvious in view of column 6, lines 54-67; column 17, lines 35-40; and Figure 9 of the instant specification which demonstrates the well-known technique of minimizing the mismatches that occur between the target sequence and its hybridization probes in order to minimize false positives (or reducing the signals from mismatched probes to a background level).

With regard to instant claims 13-14, and 16 drawn to the first and second probe being differently labeled, and the labels being Cy3 and Cy5, and the detection of different SNPs in target nucleic acid, claims 14, 16, 32, and 33 of the '742 patent, as well as on column 20 and Figure 12 of its specification discloses that at least two different SNPs (Hemocromatosis locus and Factor V locus) are identified from a sample in the multiplex analysis of target sequences.

Additionally, the method of Nerenberg et al. allows the hybridization of the probes to the target nucleic acids occur prior to the immobilization of the target nucleic acids to the test sites (as evidenced by claims 1 and 2 of Nerenberg et al.), thereby meeting instant claim 17.

With regard instant claims 19-21, drawn to repeating the SNP detection with at least one additional mixture of first and second probes, method involving stripping of the first-applied first and second probes, claim 17 of the '742 patent recites that at least one specific sequence in at least one genetic loci is "sequentially" performed, wherein the specification of the '742 patent gives such example as involving an electronic hybridization of the probes for Hemocromatosis, followed by their stripping, then followed by the electronic hybridization of the probes for Factor V (column 20, lines 10-15).

The '742 patent do not explicitly disclose the method which monitors the detectable signal from hybridization complexes between the target nucleic acid and the labeled probes, in real time during various stages of electronic hybridization and stringency in order to determine the melting point of the probes and target nucleic acid sequence (instant claim 10), wherein the power level or length of time of the electronic stringency is controlled based on the signal detection (instant claim 11).

The '742 patent do not explicitly disclose that the plurality of sample nucleic acids from each patient samples are immobilized on one test site, wherein each sample nucleic acid of each patient sample comprises a different SNP locus (instant claim 15).

The '742 patent do not explicitly disclose that the patient sample nucleic acids, after their hybridization to their probes, are sequentially immobilized onto the test sites (instant claim 18).

Heller et al. disclose a method of employing the same electronically addressable array of the '742 patent for the purpose of determining the FPE, or fluorescent perturbation effect, which is a powerful analytical tool for efficient discrimination of match/mismatch DNA hybrids (column 5, lines 15-20). The method involves the monitoring of the relative fluorescent intensity of the hybridized probes with respect to the voltage applied (Figure 1A and 1B, therefore meets instant claims 10 and 11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of the '742 patent with that of Heller et al. to arrive at the claimed invention for the following reasons.

Nerenberg et al. recgonizes the importance of being able to distinguish between the match and mismatched probes, wherein the artisans state:

"Moreoever, electronic biasing equally facilitates distinguishing hybridization mismatches occurring at the terminal nucleic acid pairs of a hybridized duplex as well as destabilizing mismatches occurring internally...allow[ing] the current invention to be less restricted in choices for positioning the location of SNP bases on probes..." (column 6, lines 54-61).

Heller et al. disclose that the fluorescent signal from labeled probes or target DNAs was perturbed during the initiation of electronic dehybridization (or stringency) ***at or around the electronic power levels (current and voltage)*** resulting as a, "rise or spike in the fluorescence intensity prior to dehybridization of the fluorescent labeled probe sequence from the DNA sequence attached to the microscopic test site (column 10, lines 40-49), allowing the

match/mismatch discrimination of the probes to be carried out, "***very rapidly***...compared to classical hybridization stringency process...." (column 11, lines 1-5).

Therefore, one of ordinary skill in the art would have been motivated to adopt the teachings of Heller et al., who employ the same electronically addressable array as Nerenberg et al. to arrive at the method of determining the FPE, for the advantage of efficiently discriminating the match and mismatch of probes-target duplex (*i.e.,* further improving the mismatch discrimination already recognized by Nerenberg et al.) with a reasonable expectation of success.

With regard to whether the plurality of sample nucleic acids from each patient samples are immobilized on one test site or different test sites, and whether each sample nucleic acid of from each patient sample comprises a different SNP locus, such is an obvious design modification that is considered to be well within the purview of an ordinarily skilled artisan in the array design (*i.e.,* Affymetrix™).

Finally, with regard to the patient sample nucleic acids, after their hybridization to their probes, being sequentially immobilized onto the test sites, as all nucleic acids must first be immobilized on to the test sites prior to their detection, one of ordinary skill in the art would have recognized that the probe-target hybridization duplex, had to be sequentially immobilized on to their test site for the subsequent detection method with a reasonable expectation of success.

In *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342 (CCPA 1968), the court expressed that, "in considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inference which one skilled in the art would reasonably be expected to draw therefrom."

Finally, in responding to Applicants' arguments stating that Affymetrix uses a system in which the capture probes are immobilized to the array not the sample nucleic acids (on page 9, 1st paragraph, Response), the example provided in the Office Action was solely intended to demonstrate whether the immobilized nucleic acids are immobilized on a single test site or across a plurality of different test sites was well-within the purview of an ordinarily skilled artisan. Applicants are reminded that in addition to Affymetrix microarrays, there is a host of well-known solid-substrate arrays which employ immobilized target nucleic acids on a solid-substrate (*i.e.,* ASO).

Therefore, it is maintained that whether an ordinarily skilled artisan would be inclined to immobilize all of the oligonucleotides on a single reaction site versus across a plurality of different reaction sites, such would be well-within the purview of said ordinarily skilled artisan.

Therefore, for the above reasons, the claims are *prima facie* obvious over the cited references.

Claim 6 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6,468,742 B2 (hereto referred to as '742 patent) in view of Heller et al. (U.S. Patent No. 6,048,690, issued April 11, 2000, filed May 14, 1997) as applied to claims 1-5, 7-9, 12-14, 16, 17, and 19-21, and further in view of Fodor et al. (U.S. Patent No. 6,309,823 B1, issued October 30, 2001, filed January 3, 1997).

Claims of the instant application is broadly drawn to a method of detecting a single nucleotide polymorphism involving the use of a microelectronic chip, utilizing electronic stringency controls.

Nerenberg et al. and Heller et al. do not disclose a method of employing at least one control target nucleic acid.

Fodor et al. disclose a method of detecting polymorphisms via use of an oligonucleotide arrays, wherein the array contains control probes, for the purpose of gauging the background intensity level (column 10, lines 31-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the well known technique of employing control probes on a microarray of Nerenberg et al. for the obvious benefit of accounting for background (or noise level) prevalent in a hybridization assay. One of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings as the use of control probes in the array hybridization, as demonstrated by Fodor et al., have been well-established in the art.

MPEP, at 2143.02, states that the prior art can be modified or combined to reject claims as obvious as long as there is a reasonable expectation of success. Given that the use of control probes in microarray for the benefit of accounting for background hybridization has been well-established, one of ordinary skill in the art microarray would have had a reasonable expectation of the success in making design modification to achieve the same method with a reasonable expectation of success, rendering the claims obvious over the cited references.

Finally, in responding to Applicants' arguments stating that Affymetrix uses a system in which the capture probes are immobilized to the array not the sample nucleic acids (on page 9,

1st paragraph, Response), the example provided in the Office Action was solely intended to demonstrate whether the immobilized nucleic acids are immobilized on a single test site or across a plurality of different test sites was well-within the purview of an ordinarily skilled artisan. Applicants are reminded that in addition to Affymetrix microarrays, there is a host of well-known solid-substrate arrays which employ immobilized target nucleic acids on a solid-substrate (*i.e.,* ASO).

Therefore, it is maintained that whether an ordinarily skilled artisan would be inclined to immobilize all of the oligonucleotides on a single reaction site versus across a plurality of different reaction sites, such would be well-within the purview of said ordinarily skilled artisan.

Therefore, for the above reasons, the claims are *prima facie* obvious over the cited references.

Rejection – Maintained

The rejection of claims 11 and 18 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6,468,742 B2 (hereto referred to as '742 patent) in view of Heller et al. (U.S. Patent No. 6,048,690, issued April 11, 2000, filed May 14, 1997), made in the Office Action mailed on May 3, 2004 is maintained for the reasons of record.

Applicants' arguments received on November 5, 2004 have been fully considered but they are not found persuasive.

Preliminarily, Applicants are advised that claims 11 and 18 were rejected along with claims 10 and 15 as being obvious over the above cited references. Hence, the rejection is

properly maintainable although claim limitations of claims 10 and 15 were incorporated into independent claim 1.

Applicants argue that Affymetrix uses a system in which the capture probes are immobilized to the array not the sample nucleic acids (on page 9, 1st paragraph, Response), the example provided in the Office Action was solely intended to demonstrate whether the immobilized nucleic acids are immobilized on a single test site or across a plurality of different test sites was well-within the purview of an ordinarily skilled artisan. Applicants are reminded that in addition to Affymetrix microarrays, there is a host of well-known solid-substrate arrays which employ immobilized target nucleic acids on a solid-substrate (*i.e.*, ASO).

Therefore, it is maintained that whether an ordinarily skilled artisan would be inclined to immobilize all of the oligonucleotides on a single reaction site versus across a plurality of different reaction sites, such would be well-within the purview of said ordinarily skilled artisan.

Therefore, for the above reasons, the claims are *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a

general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

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Young J. Kim
Patent Examiner
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2/9/05

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PATENT EXAMINER

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